Copy for the Elected Office (EO/US)

PATENT COOPERATION TREAT

09/762391

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

MARTIN, Jean-Jacques
Cabinet Regimbeau
20, rue de Chazelles
F-75847 Paris Cedex 17
FRANCE

Date of mailing (day/month/year)
12 March 2001 (12.03.01)

IMPORTANT NOTIFICATION

Applicant's or agent's file reference
340115/18363

International application No.
PCT/IB99/01444

International filing date (day/month/year)
06 August 1999 (06.08.99)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
MARTIN, Jean-Jacques
Cabinet Regimbeau
26, avenue Kléber
F-75116 Paris
France

State of Nationality:
State of Residence:
Telephone No.: 01 45 00 92 02
Facsimile No.: 01 45 00 46 12
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
MARTIN, Jean-Jacques
Cabinet Regimbeau
20, rue de Chazelles
F-75847 Paris Cedex 17
France

State of Nationality:
State of Residence:
Telephone No.: 01-44-29-35-00
Facsimile No.: 01-44-29-35-99
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Maria Victoria CORTIELLO

Telephone No.: (41-22) 338.83.38

003889352

Form PCT/IB/306 (March 1994)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 March 2000 (22.03.00)	
International application No. PCT/IB99/01444	**Applicant's or agent's file reference** 340115/18363
International filing date (day/month/year) 06 August 1999 (06.08.99)	**Priority date** (day/month/year) 07 August 1998 (07.08.98)
Applicant BLUMENFELD, Marta et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

28 February 2000 (28.02.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Jean-Marc Vivet

Telephone No.: (41-22) 338.83.38

3182094

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C12Q 1/68, C12N 15/63, 15/85

A3

(11) International Publication Number: **WO 00/08209**

(43) International Publication Date: 17 February 2000 (17.02.00)

(21) International Application Number: PCT/IB99/01444

(22) International Filing Date: 6 August 1999 (06.08.99)

(30) Priority Data:
60/095,653 7 August 1998 (07.08.98) US

(71) Applicant *(for all designated States except US)*: GENSET [FR/FR]; 24, rue Royale, F–75008 Paris (FR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BLUMENFELD, Marta [FR/FR]; 5, rue Tagore, F–75013 Paris (FR). BOUGUELERET, Lydie [FR/FR]; 14, rue Vouillé, F–75015 Paris (FR). CHUMAKOV, Ilya [FR/FR]; 196, rue des Chèvrefeuilles, F–77000 Vaux–le–Pénil (FR).

(74) Agents: MARTIN, Jean–Jacques et al.; Cabinet Regimbeau, 26, avenue Kléber, F–75116 Paris (FR).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
9 November 2000 (09.11.00)

(54) Title: NUCLEIC ACIDS ENCODING HUMAN TBC–1 PROTEIN AND POLYMORPHIC MARKERS THEREOF

(57) Abstract

The invention concerns genomic and cDNA sequences of the human *TBC–1* Gene. The invention also concerns polypeptides encoded by the *TBC–1* gene. The invention also deals with antibodies directed specifically against such polypeptides that are useful as diagnostic reagents. The invention further encompasses biallelic markers of the *TBC–1* gene useful in genetic analysis.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/01444

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 20165 A (WHITEHEAD BIOMEDICAL INST ;HUDSON THOMAS (US); LANDER ERIC S (US);) 14 May 1998 (1998-05-14) * see especially page 19, line 12 to page 20, line 3, as well as the claims * the whole document	
A	BERTHON P ET AL: "PREDISPOSING GENE FOR EARLY-ONSET PROSTATE CANCER, LOCALIZED ON CHROMOSOME 1Q42.2-43" AMERICAN JOURNAL OF HUMAN GENETICS,US,UNIVERSITY OF CHICAGO PRESS, CHICAGO,, vol. 62, no. 6, June 1998 (1998-06), pages 1416-1424, XP000857378 ISSN: 0002-9297 the whole document	
A	FAN J ET AL: "Genetic mapping: Finding and analyzing single-nucleotide polymorphisms with high-density DNA arrays" AMERICAN JOURNAL OF HUMAN GENETICS,US,UNIVERSITY OF CHICAGO PRESS, CHICAGO,, vol. 61, no. 4, SUPPL, 1 October 1997 (1997-10-01), page 1601 XP002089397 ISSN: 0002-9297 abstract	
P,X	WO 99 32644 A (BOUGUELERET LYDIE ;CHUMAKOV ILYA (FR); COHEN DANIEL (FR); GENSET ( ) 1 July 1999 (1999-07-01) the whole document	1-5,7,8, 10-13, 17-38

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 99/01444

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5700927 A	23-12-1997	NONE	
WO 9820165 A	14-05-1998	EP 0941366 A	15-09-1999
WO 9932644 A	01-07-1999	US 5945522 A	31-08-1999
		AU 1574099 A	12-07-1999
		EP 0991770 A	12-04-2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
340115/18363		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB99/01444	06/08/1999	07/08/1998
International Patent Classification (IPC) or national classification and IPC		
C12Q1/68		
Applicant		
GENSET et. al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28/02/2000	24.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Thiele, U Telephone No. +49 89 2399 8643

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/01444

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-80	as originally filed				

Claims, No.:

1-36	as received on	13/11/2000	with letter of	10/11/2000	

Drawings, sheets:

1/5-5/5	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-36
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36

Industrial applicability (IA) Yes: Claims 1-36
No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section I

1) Under Rule 13ter.(f) PCT, sequence listings filed after the filing date of the application (here 05.01.2000) do not form part of the description and will not be annexed to this opinion / report.

2) Sequence listing pages 1 - 75 as originally filed are included in the basis of this opinion / report.

3) The amendments filed with the letter dated 10.11.2000 comply with the requirements of Art. 34(2)(b) PCT.

Section IV

The application lacks unity within the meaning of Article 13 PCT.

Sequences falling within the scope of claims 1 - 4 lack an inventive step (see section V, item 3, below). The general concept of sequences containing contiguous spans of nucleotides of SEQ IDs 1 - 4 is known. The requirements of unity of invention are thus not fulfilled in that there is no technical relationship among the inventions as they do not involve one or more of the same or corresponding special technical features.

Consequently, there is multiple non-unity of invention for the product claims. In addition, uses of the products are non-unitarian.

Section V

1) Reference is made to the following documents:

D1 EMBL genebank AC X40323 & WO-A-9 906 439
D2 EMBL genebank AC Z41904
D3 EMBL genebank AC AA346082

D4 EMBL genebank Z78359
D5 EMBL genebank H62992
D6 EMBL genebank AA804534
D7 US-A-5 700 927, cited in the application on page 18
D8 SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, vol. 280, 1998, pages 1077-1082
D9 AMERICAN JOURNAL OF HUMAN GENETICS,US,UNIVERSITY OF CHICAGO PRESS, CHICAGO, vol. 61, no. 4, SUPPL, 1 October 1997

The documents D1 - D6 were not cited in the international search report.

2) The subject-matter of claims 1 - 36 would appear to be novel for not being disclosed in any of the known prior art documents (Art. 33(2) PCT).

3) The subject-matter of claims 1 - 4 although being formally new, is considered to lack the presence of inventive step (Art. 33(3) PCT).

The sequences disclosed in D2 - D7 would appear to disclose sequences presenting 100% identity with the SEQ IDs 1 - 4 at maximum 51 bp length (see also applicant's letter of 10.11.2000).

The applicant in the present description, see e.g. page 49, considers contiguous spans of between 12 and 1000 nucleotides of the particular SEQ IDs as being equally well suited within the framework of the present invention.

Thus, the particular contiguous span claimed would appear not to result in any unexpected effects whatsoever, and would appear to merely result from an arbitrary selection of sequence length values.

4) It would appear that the present invention relates to an allegedly previously unknown **candidate** region of prostate cancer located on human chromosome 4 (see page 4, lines 17 et seq. of the present application; page 18, first paragraph). The present applicants have identified said candidate region by linkage analysis (page 17, last paragraph). A gene, TBC-1, which allegedly presents a **good probability** to be involved in cancer was found in this candidate region (emphasis

added).

The application is, however, devoid of any technical data whatsoever as to the clinical implications in terms of diagnosis and therapy of TBC-1. Thus, there is no disclosure of the industrial application of neither the gene nor the partial sequence of the gene in the application. No unified criteria in this respect exist in the PCT Contracting States. The EPO, for example, does not recognize as patentable such subject-matter.

5) The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of claim 5 does not involve an inventive step (Rule 65(1)(2) PCT).

In the absence of technical data providing evidence for a particular functionality or diagnostic / therapeutic relevance of human TBC-1, the IPEA has to assume that this particular gene is not the result of a guided selection. The skilled person, being equipped with the teaching of D8 taken in combination with D9 would, thus, have had enough guidance and motivation to carry out the large-scale genotyping of polymorphisms disclosed therein also on this known part (see D2 - D6) of the human genome, and would thus have arrived with a high expectation of success at the subject-matter of claim 5 already for this reason alone.

A further incentive to identify biallelic markers in the human TBC-1 can be deduced from D7 (see e.g. col. 2, bottom line; col. 11, line 25), where the diagnostic and therapeutic value of human TBC-1 in relation to leukemia is anticipated. The main focus of D7 is on the sequence of murine tbc1. In D7, however, chromosomal localization of murine and human tbc1 is addressed (see col. 10, lines 30 et seq.).

6) In view of the remarks made under item 4, above, in addition, no inventive step can be acknowledged for the subject-matter of claims 7, 8, 10 - 13, 16 and 17 - 33 which in essence relates back to TBC-1 biallelic markers. The additional technical features would appear to merely be within the routine skills of those in the art. Deducing the amino acid sequence of a known nucleic acid sequence (see D2 - D6) does not require inventive activity (see present claim 16).

7) The particular biallelic markers of claims 6, 9, 14, 15 and 34 would appear to be the inevitable result of the methodical approaches discussed under item 5, supra, and would thus appear to analogously lack an inventive step (Art. 33(3) PCT).

8) Lastly, also the subject-matter of claims 35 and 36 is considered not involve an inventive step (Art. 33(3) PCT).

It is considered conventional in the technical field concerned to deduce the amino acid sequence encoded by a nucleic acid sequence.

Moreover, it is conventional in the technical field concerned to generate antibodies and corresponding polypeptide fragments of an amino acid sequence in order to e.g. carry out epitope mapping.

Thus, it would appear that the subject-matter of claims 35 and 36 is merely directed to conventional products which are the result of an arbitrary selection of many more analogous products possible. In the absence of a technical problem solved in an unexpected way in relation to **particular** non-obvious polypeptides or antibodies, the presence of an inventive step cannot be acknowledged.

Section VI

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document D1 (WO-A-9 906 439), and the document WO-A-9 932 644 cited in the International Search Report, which both have been published after the priority date of the present application, could become relevant.

Section VII

1) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 - D9 is not mentioned in the description, nor are these documents identified therein.

2) The statement in the description, paragraph bridging over pages 71 and 72, does not comply the requirement that the application has to be self-contained (see Guidelines, II, 4.17).

Section VIII

1) The terms "polynucleotide consists/consisting essentially of [...]" as used in claims 5, 9, 12 and 14 render the scope of the claims concerned indeterminate (Art. 6 PCT).

2) In claim 5 and throughout the further claims the term TBC-1 is a trivial designation attributed to an allegedly novel gene by the applicant himself. In the absence of reference to a SEQ ID, the said term is thus meaningless to the skilled person and consequently renders the scope of the claims concerned unclear (Art. 6 PCT). It is not clear from the wording "TBC-1 related biallelic marker" what is the identity of the sequence named TBC-1.

3) The term biallelic marker is not precisely defined in the present application (see page 11, first paragraph). The wording "having two alleles at a fairly high frequency in the population" is vague and open to interpretation. The following sentence which merely refers to typical frequencies is not suitable for further defining the term objected to.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/01444

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C12N15/63 C12N15/85

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
STRAND, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 700 927 A (ZON LEONARD ET AL) 23 December 1997 (1997-12-23) cited in the application the whole document ---	
A	WANG D G ET AL: "Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome" SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 280, 1998, pages 1077-1082, XP002089398 ISSN: 0036-8075 the whole document --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2000	10/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Knehr, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/IB 99/01444

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C12N15/63 C12N15/85

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
STRAND, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 700 927 A (ZON LEONARD ET AL) 23 December 1997 (1997-12-23) cited in the application the whole document ---	
A	WANG D G ET AL: "Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome" SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 280, 1998, pages 1077-1082, XP002089398 ISSN: 0036-8075 the whole document --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2000	10/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Knehr, M

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]T/IB 99/01444

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 20165 A (WHITEHEAD BIOMEDICAL INST ;HUDSON THOMAS (US); LANDER ERIC S (US);) 14 May 1998 (1998-05-14) * see especially page 19, line 12 to page 20, line 3, as well as the claims * the whole document	
A	BERTHON P ET AL: "PREDISPOSING GENE FOR EARLY-ONSET PROSTATE CANCER, LOCALIZED ON CHROMOSOME 1Q42.2-43" AMERICAN JOURNAL OF HUMAN GENETICS,US,UNIVERSITY OF CHICAGO PRESS, CHICAGO,, vol. 62, no. 6, June 1998 (1998-06), pages 1416-1424, XP000857378 ISSN: 0002-9297 the whole document	
A	FAN J ET AL: "Genetic mapping: Finding and analyzing single-nucleotide polymorphisms with high-density DNA arrays" AMERICAN JOURNAL OF HUMAN GENETICS,US,UNIVERSITY OF CHICAGO PRESS, CHICAGO,, vol. 61, no. 4, SUPPL, 1 October 1997 (1997-10-01), page 1601 XP002089397 ISSN: 0002-9297 abstract	
P,X	WO 99 32644 A (BOUGUELERET LYDIE ;CHUMAKOV ILYA (FR); COHEN DANIEL (FR); GENSET ()) 1 July 1999 (1999-07-01) the whole document	1-5,7,8, 10-13, 17-38

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
T/IB 99/01444

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5700927	A	23-12-1997	NONE		
WO 9820165	A	14-05-1998	EP	0941366 A	15-09-1999
WO 9932644	A	01-07-1999	US	5945522 A	31-08-1999
			AU	1574099 A	12-07-1999
			EP	0991770 A	12-04-2000

PATENT COOPERATION TREATY

REC'D 28 NOV 2000
IPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
340115/18363		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB99/01444	06/08/1999	07/08/1998
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant GENSET et. al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28/02/2000	24.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Thiele, U Telephone No. +49 89 2399 8643

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/01444

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-80 as originally filed

Claims, No.:

1-36 as received on 13/11/2000 with letter of 10/11/2000

Drawings, sheets:

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-36
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36

Industrial applicability (IA)	Yes:	Claims	1-36
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section I

1) Under Rule 13ter.(f) PCT, sequence listings filed after the filing date of the application (here 05.01.2000) do not form part of the description and will not be annexed to this opinion / report.

2) Sequence listing pages 1 - 75 as originally filed are included in the basis of this opinion / report.

3) The amendments filed with the letter dated 10.11.2000 comply with the requirements of Art. 34(2)(b) PCT.

Section IV

The application lacks unity within the meaning of Article 13 PCT.

Sequences falling within the scope of claims 1 - 4 lack an inventive step (see section V, item 3, below). The general concept of sequences containing contiguous spans of nucleotides of SEQ IDs 1 - 4 is known. The requirements of unity of invention are thus not fulfilled in that there is no technical relationship among the inventions as they do not involve one or more of the same or corresponding special technical features.

Consequently, there is multiple non-unity of invention for the product claims. In addition, uses of the products are non-unitarian.

Section V

1) Reference is made to the following documents:

D1 EMBL genebank AC X40323 & WO-A-9 906 439
D2 EMBL genebank AC Z41904
D3 EMBL genebank AC AA346082

D4 EMBL genebank Z78359
D5 EMBL genebank H62992
D6 EMBL genebank AA804534
D7 US-A-5 700 927, cited in the application on page 18
D8 SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, vol. 280, 1998, pages 1077-1082
D9 AMERICAN JOURNAL OF HUMAN GENETICS,US,UNIVERSITY OF CHICAGO PRESS, CHICAGO, vol. 61, no. 4, SUPPL, 1 October 1997

The documents D1 - D6 were not cited in the international search report.

2) The subject-matter of claims 1 - 36 would appear to be novel for not being disclosed in any of the known prior art documents (Art. 33(2) PCT).

3) The subject-matter of claims 1 - 4 although being formally new, is considered to lack the presence of inventive step (Art. 33(3) PCT).

The sequences disclosed in D2 - D7 would appear to disclose sequences presenting 100% identity with the SEQ IDs 1 - 4 at maximum 51 bp length (see also applicant's letter of 10.11.2000).

The applicant in the present description, see e.g. page 49, considers contiguous spans of between 12 and 1000 nucleotides of the particular SEQ IDs as being equally well suited within the framework of the present invention.

Thus, the particular contiguous span claimed would appear not to result in any unexpected effects whatsoever, and would appear to merely result from an arbitrary selection of sequence length values.

4) It would appear that the present invention relates to an allegedly previously unknown **candidate** region of prostate cancer located on human chromosome 4 (see page 4, lines 17 et seq. of the present application; page 18, first paragraph). The present applicants have identified said candidate region by linkage analysis (page 17, last paragraph). A gene, TBC-1, which allegedly presents a **good probability** to be involved in cancer was found in this candidate region (emphasis

added).

The application is, however, devoid of any technical data whatsoever as to the clinical implications in terms of diagnosis and therapy of TBC-1. Thus, there is no disclosure of the industrial application of neither the gene nor the partial sequence of the gene in the application. No unified criteria in this respect exist in the PCT Contracting States. The EPO, for example, does not recognize as patentable such subject-matter.

5) The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of claim 5 does not involve an inventive step (Rule 65(1)(2) PCT).

In the absence of technical data providing evidence for a particular functionality or diagnostic / therapeutic relevance of human TBC-1, the IPEA has to assume that this particular gene is not the result of a guided selection. The skilled person, being equipped with the teaching of D8 taken in combination with D9 would, thus, have had enough guidance and motivation to carry out the large-scale genotyping of polymorphisms disclosed therein also on this known part (see D2 - D6) of the human genome, and would thus have arrived with a high expectation of success at the subject-matter of claim 5 already for this reason alone.

A further incentive to identify biallelic markers in the human TBC-1 can be deduced from D7 (see e.g. col. 2, bottom line; col. 11, line 25), where the diagnostic and therapeutic value of human TBC-1 in relation to leukemia is anticipated. The main focus of D7 is on the sequence of murine tbc1. In D7, however, chromosomal localization of murine and human tbc1 is addressed (see col. 10, lines 30 et seq.).

6) In view of the remarks made under item 4, above, in addition, no inventive step can be acknowledged for the subject-matter of claims 7, 8, 10 - 13, 16 and 17 - 33 which in essence relates back to TBC-1 biallelic markers. The additional technical features would appear to merely be within the routine skills of those in the art. Deducing the amino acid sequence of a known nucleic acid sequence (see D2 - D6) does not require inventive activity (see present claim 16).

7) The particular biallelic markers of claims 6, 9, 14, 15 and 34 would appear to be the inevitable result of the methodical approaches discussed under item 5, supra, and would thus appear to analogously lack an inventive step (Art. 33(3) PCT).

8) Lastly, also the subject-matter of claims 35 and 36 is considered not involve an inventive step (Art. 33(3) PCT).

It is considered conventional in the technical field concerned to deduce the amino acid sequence encoded by a nucleic acid sequence.

Moreover, it is conventional in the technical field concerned to generate antibodies and corresponding polypeptide fragments of an amino acid sequence in order to e.g. carry out epitope mapping.

Thus, it would appear that the subject-matter of claims 35 and 36 is merely directed to conventional products which are the result of an arbitrary selection of many more analogous products possible. In the absence of a technical problem solved in an unexpected way in relation to **particular** non-obvious polypeptides or antibodies, the presence of an inventive step cannot be acknowledged.

Section VI

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document D1 (WO-A-9 906 439), and the document WO-A-9 932 644 cited in the International Search Report, which both have been published after the priority date of the present application, could become relevant.

Section VII

1) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 - D9 is not mentioned in the description, nor are these documents identified therein.

2) The statement in the description, paragraph bridging over pages 71 and 72, does not comply the requirement that the application has to be self-contained (see Guidelines, II, 4.17).

Section VIII

1) The terms "polynucleotide consists/consisting essentially of [...]" as used in claims 5, 9, 12 and 14 render the scope of the claims concerned indeterminate (Art. 6 PCT).

2) In claim 5 and throughout the further claims the term TBC-1 is a trivial designation attributed to an allegedly novel gene by the applicant himself. In the absence of reference to a SEQ ID, the said term is thus meaningless to the skilled person and consequently renders the scope of the claims concerned unclear (Art. 6 PCT). It is not clear from the wording "TBC-1 related biallelic marker" what is the identity of the sequence named TBC-1.

3) The term biallelic marker is not precisely defined in the present application (see page 11, first paragraph). The wording "having two alleles at a fairly high frequency in the population" is vague and open to interpretation. The following sentence which merely refers to typical frequencies is not suitable for further defining the term objected to.

CLAIMS

1. An isolated, purified, or recombinant polynucleotide comprising a contiguous span of at least 60 nucleotides of SEQ ID No. 1 or the complements thereof.

2. An isolated, purified, or recombinant polynucleotide comprising a contiguous span of at least 60 nucleotides of SEQ ID No. 2 or the complements thereof.

3. An isolated, purified, or recombinant polynucleotide comprising a contiguous span of at least 60 nucleotides of SEQ ID No. 3 or the complements thereof.

4. An isolated, purified, or recombinant polynucleotide comprising a contiguous span of at least 60 nucleotides of SEQ ID No 4. or the complements thereof.

5. An isolated, purified, or recombinant polynucleotide consisting essentially of a contiguous span of 8 to 50 nucleotides of anyone of SEQ ID Nos. 1 and 2 or the complement thereof, wherein said span includes a *TBC-1*-related biallelic marker in said sequence.

6. A polynucleotide according to claim 5, wherein said *TBC-1*-related biallelic marker is selected from the group consisting of the biallelic markers in positions 9494 of the SEQ ID No. 1, and 1443, 5247, 6223, 14723, 19186, 18997, 19891, 29617, 42519, 69324, 69181, 69146, 76458, 78595, 82159, 84522, 84810, and 89967 of the SEQ ID No. 2.

7. A polynucleotide according to any one of claims 5 or 6, wherein said contiguous span is 18 to 35 nucleotides in length and said biallelic marker is within 4 nucleotides of the center of said polynucleotide.

8. A polynucleotide according to claim 7, wherein said polynucleotide consists of said contiguous span and said contiguous span is 25 nucleotides in length and said biallelic marker is at the center of said polynucleotide.

9. A polynucleotide according to claim 8, wherein said polynucleotide consists essentially of a sequence selected from the sequences with the position range 9482-9506 in SEQ ID No. 1 and with the following position ranges in SEQ ID No. 2 : 1431-1455, 5235-5259, 6211-6235, 14711-14735, 19174-19198, 18985-19009, 29605-29629, 42507-42531, 69312-69336, 69169-69193, 69134-69158, 78583-78607, 82147-82171, 84510-84534, 84798-84822, and 89955-89979, and the complementary sequences thereto.

10. A polynucleotide according to any one of claims 1 to 6, wherein the 3' end of said contiguous span is present at the 3' end of said polynucleotide.

11. A polynucleotide according to any one of claims 5 or 6, wherein the 3' end of said contiguous span is located at the 3' end of said polynucleotide and said biallelic marker is present at the 3' end of said polynucleotide.

12. An isolated, purified, or recombinant polynucleotide consisting essentially of a contiguous span of 8 to 50 nucleotides of anyone of SEQ ID Nos. 1 and 2 or the complement thereof, wherein the 3' end of said contiguous span is located at the 3' end of said polynucleotide,

and wherein the 3' end of said polynucleotide is located within 20 nucleotides upstream of a *TBC-1*-related biallelic marker in said sequence.

13. A polynucleotide according to claim 12, wherein the 3' end of said polynucleotide is located 1 nucleotide upstream of said *TBC-1*-related biallelic marker in said sequence.

14. A polynucleotide according to claim 13, wherein said polynucleotide consists essentially of a sequence selected from the sequences with the position range 9475-9493 in SEQ ID No. 1 and with the following position ranges in SEQ ID No 2 : 1424-1442, 5228-5246, 6204-6222, 14704-14722, 19167-19185, 18978-18996, 19872-19890, 29598-29616, 42500-42518, 69305-69323, 69162-69180, 69127-69145, 76439-76457, 78576-78594, 82140-82158, 84503-84521, 84791-84809, and 89948-89966, and the complementary position range 9495-9513 in SEQ ID No. 1 and the following complementary position ranges in SEQ ID No 2 : 1444-1462, 5248-5266, 6224-6242, 14724-14742, 19187-19205, 18998-19016, 19892-19910, 29618-29636, 42520-42538, 69325-69343, 69182-69200, 69147-69165, 76459-76477, 78596-78614, 82160-82178, 84523-84541, 84811-84829, and 89968-89986.

15. An isolated, purified, or recombinant polynucleotide consisting essentially of a sequence selected from the sequences with the position range 9391-9408 in SEQ ID No 1 and with the following position ranges in SEQ ID No 2 : 988-1006, 5039-5056, 5997-6015, 14371-14390, 18751-18771, 19605-19625, 29529-29547, 42268-42287, 69026-69046, 76323-76343, 78292-78309, 81893-81912, 84392-84412, and 89746-89765, and the complementary position range 9828-9845 in SEQ ID No 1 and the following complementary position ranges in SEQ ID No 2 : 1509-1529, 5534-5554, 6332-6350, 14798-14817, 19198-19217, 19986-20005, 30041-30061, 42732-42752, 69525-69543, 76771-76790, 78704-78721, 82353-82372, 84909-84929, and 90179-90198.

16. An isolated, purified, or recombinant polynucleotide which encodes a polypeptide comprising a contiguous span of at least 6 amino acids of SEQ ID No 5.

17. A polynucleotide according to any one of claims 1 to 16 attached to a solid support.

18. An array of polynucleotides comprising at least one polynucleotide according to claim 17.

19. An array according to claim 18, wherein said array is addressable.

20. A polynucleotide according to any one of claims 1 to 16 further comprising a label.

21. A recombinant vector comprising a polynucleotide according to any one of claims 1 to 4 and 16.

22. A host cell comprising a recombinant vector according to claim 21.

23. A non-human host animal or mammal comprising a recombinant vector according to claim 22.

24. A method of genotyping comprising determining the identity of a nucleotide at a *TBC-1*-related biallelic marker or the complement thereof in a biological sample.

25. A method according to claim 24, wherein said biological sample is derived from a single subject.

26. A method according to claim 25, wherein the identity of the nucleotides at said biallelic marker is determined for both copies of said biallelic marker present in said individual's genome.

27. A method according to claim 24, wherein said biological sample is derived from multiple subjects.

28. A method according to claim 24, further comprising amplifying a portion of said sequence comprising the biallelic marker prior to said determining step.

29. A method according to claim 28, wherein said amplifying is performed by PCR.

30. A method according to claim 24, wherein said determining is performed by a hybridization assay.

31. A method according to claim 24, wherein said determining is performed by a sequencing assay.

32. A method according to claim 24, wherein said determining is performed by a microsequencing assay.

33. A method according to claim 24, wherein said determining is performed by an enzyme-based mismatch detection assay.

34. A method according to any one of claims 24 to 33 wherein said *TBC-1*-related biallelic marker is selected from the group consisting of the biallelic markers in positions 9494 of the SEQ ID No. 1, and 1443, 5247, 6223, 14723, 19186, 18997, 19891, 29617, 42519, 69324, 69181, 69146, 76458, 78595, 82159, 84522, 84810, and 89967 of the SEQ ID No. 2.

35. An isolated, purified, or recombinant polypeptide comprising a continuous span of at least 8 amino acids of SEQ ID No 5.

36. An isolated or purified antibody composition capable of selectively binding to an epitope-containing fragment of a polypeptide according to claim 35.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
340115/18363		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 99/ 01444	06/08/1999	07/08/1998
Applicant		
GENSET et. al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.